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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,216	01/20/2004	Stephen F. Kingsmore	36671-747.201	6434

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EXAMINER	
GANGLE, BRIAN J	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
06/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,216	KINGSMORE ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-23 and 96-108* is/are pending in the application.

4a) Of the above claim(s) *5,6,9-18,20-23 and 96-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/8/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/6/2009 has been entered.

The amendment and remarks, filed 3/6/2009, are acknowledged. Claims 1 and 19 are amended. Claims 1-6, 8-23, and 96-108 are pending. Claims 5-6, 9-18, 20-23, and 96-108 are withdrawn as being drawn to non-elected inventions. Claims 1-4, 8, and 19 are currently under examination.

Information Disclosure Statement

The information disclosure statement filed on 12/8/2009 has been considered. An initialed copy is enclosed.

Objections Withdrawn

The objection to the drawings as failing to comply with 37 CFR 1.84(p)(5), because they include the following reference character(s) not mentioned in the description: 5A-5E and 6A-6E, is withdrawn in light of applicant's amendment to the specification.

The objection to the drawings as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: Figure 9, is withdrawn in light of applicant's amendment to the specification.

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: Figures 11, 12, and 14, is withdrawn in light of applicant's amendment to the specification.

Claim Rejections Withdrawn

The rejection of claims 1-4, 8, and 19 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is withdrawn upon reconsideration and based on some of applicant's arguments. On page 14 of the response, applicant asserts that the methods utilize markers as clinical criteria that provide key information on the degree of systemic inflammation in a patient suspected of having severe sepsis and emphasize that MPIF-1 and TNF-R1 are *indicative* of severe sepsis. What has been at issue in this rejection is whether or not elevated levels of MPIF-1 and TNF-R1 show that a person has sepsis (or severe sepsis in the amended claims). It is clear from the art and the specification that both markers are elevated in conditions other than severe sepsis, and this is the reason the examiner has rejected the claims. However, upon reconsideration of the definitions of the terms "diagnose" and "indicate" the examiner agrees that the claims are enabled. The specification lacks a definition of either term; therefore, the dictionary definition of both terms is being used by the examiner. The term "diagnose" means "to distinguish or identify" or "to analyze the nature or cause of" (American Heritage Dictionary of the English Language, Fourth Ed., 2000, accessed online 2/26/2009, http://www.bartleby.com/61/40/D0194000.html). The term "indicate" is defined by the same dictionary as "to serve as a sign, symptom, or token of" (American Heritage Dictionary of the English Language, Fourth Ed., 2000, accessed online 2/26/2009, http://www.bartleby.com/61/46/I0104600.html). Therefore, while the use of the claimed method, alone, cannot determine whether a patient has severe sepsis, it can be used to analyze the nature or cause of severe sepsis, where the levels of MPIF-1 and TNF-R1 serve as a symptom of severe sepsis (i.e., the method can be used to diagnose severe sepsis and the levels of MPIF-1 and TNF-R1 can indicate the presence of severe sepsis).

New Claim Rejections

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined

application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 8, and 19 are directed to an invention not patentably distinct from claims 1-5, 10, 15, 18, and 20-28 of commonly assigned application 11/543,312; claims 1 and 12 of commonly assigned application 11/690,767; and claims 1, 12, and 19 of commonly assigned application 11/770,608. The claims are not considered to be distinct for the reasons set forth below in the double patenting rejections.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned applications 11/543,312, 11/690,767, and 11/770,608, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Claims 1-4, 8, and 19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 10, 15, 18, and 20-28 of copending Application No. 11/543,312. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

The instant claims are drawn to methods of diagnosing severe sepsis in a human subject comprising determining the concentration of MPIF-1 (and TNF-R1) in a fluid test sample from a human subject and comparing the concentration of said analytes to a reference concentration so that the concentration of the analyte in the test sample is indicative of the presence of severe sepsis.

The claims of copending application 11/543,312 are drawn to methods of diagnosing severe sepsis by assaying CCL23 (which is an alternate name for MPIF-1) and sTNFR1a and diagnosing the presence of severe sepsis. The claims also include limitations where the sample is blood, serum, or plasma. This method would necessarily include a comparison to a reference concentration to determine whether the level was high enough to warrant the diagnosis.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-4 and 19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 12 of copending Application No. 11/690,767. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

The instant claims are drawn to methods of diagnosing severe sepsis in a human subject comprising determining the concentration of MPIF-1 (and TNF-R1) in a fluid test sample from a human subject and comparing the concentration of said analytes to a reference concentration so that the concentration of the analyte in the test sample is indicative of the presence of severe sepsis.

The claims of copending application 11/690,767 are drawn to methods of assigning a prognostic risk of sepsis progression (including severe sepsis) in a subject with systemis inflammatory response by assaying CCL23 (which is an alternate name for MPIF-1) and

sTNFR1a and diagnosing the presence of severe sepsis. The claims also include limitations where the sample is blood, serum, or plasma. This method would necessarily include a comparison to a reference concentration to determine whether the level was high enough to warrant the diagnosis and the method is also necessarily a determination of the presence of severe sepsis.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-4, 8, and 19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 12, and 19 of copending Application No. 11/770,608. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

The instant claims are drawn to methods of diagnosing severe sepsis in a human subject comprising determining the concentration of MPIF-1 (and TNF-R1) in a fluid test sample from a human subject and comparing the concentration of said analytes to a reference concentration so that the concentration of the analyte in the test sample is indicative of the presence of severe sepsis.

The claims of copending application 11/770,608 are drawn to methods of diagnosing severe sepsis by assaying CCL23 (which is an alternate name for MPIF-1) and sTNFR1a and diagnosing the presence of severe sepsis. The claims also include limitations where the sample is blood, serum, or plasma. This method would necessarily include a comparison to a reference concentration to determine whether the level was high enough to warrant the diagnosis.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8, and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to methods of diagnosing severe sepsis in a human subject comprising determining a concentration of at least one analyte (MPIF-1 and TNF-R1) in a fluid test sample, comparing the concentration of said analytes to a corresponding reference concentration selected to indicate the presence or absence of severe sepsis, wherein said reference concentration is determined using one or more control samples obtained from one or more human subjects not suffering from sepsis, wherein the concentration of said analyte in the test sample relative to the reference concentration is indicative of the presence of severe sepsis in the human, and diagnosing severe sepsis in the human using the results of said comparing step.

The specification discloses information about sepsis, which is defined in the specification as an infection-induced syndrome involving two or more of the following features of systemic inflammation: fever or hypothermia, leukocytosis or leukopenia, tachycardia, and tachypnea or a supranormal minute ventilation. Severe sepsis is defined as sepsis associated with acute organ dysfunction. The specification teaches that there are multiple biomarkers that have been associated with sepsis, mostly these are cytokines associated with inflammation. Of these cytokines, some information is given on myeloid progenitor inhibitory factor-1 (MPIF-1) and tumor necrosis factor receptor-1 (TNF-R1). MPIF-1 is a cytokine that binds to CCR1. The specification states that there is no literature describing a direct association between MPIF-1 levels and sepsis, which concurs with the examiner's findings. Of TNF-R1, the specification states, "soluble TNF receptor levels were elevated in trauma patients compared to healthy persons. Severe trauma led to enhanced sTNF-R1 levels on scene and on hospital admission." Increased TNF-R1 levels are also associated with sepsis. The specification provides several studies where the levels of various biomarkers were determined in patients with sepsis and compared to those in patients without sepsis. Statistical evaluations of these data are presented which show conflicting results. Three studies were undertaken to identify suitable biomarkers for the diagnosis of sepsis. For MPIF-1, study 1 showed a significant difference between healthy

and septic individuals in both serum and plasma samples. However, study 2 showed the increase only in plasma and not in serum. Also, TNF-R1 was not identified in either study as a potential marker. In study 3, MPIF-R1 was increased in septic individuals, as was TNF-R1. The specification addresses the differences in results by listing the differences between the studies. Studies 1 and 2 were small, involving 6 and 12 patients, respectively; whereas study 3 involved 240 sepsis patients. In study 3, the patients had more severe sepsis than those in studies 1 and 2. In addition, the comparisons in studies 1 and 2 were between healthy patients and septic patients, while in study 3, the comparison was between ill, but non-septic patients and septic patients. Finally, studies 1 and 2 involved plasma and serum samples, while study 3 involved diluted serum.

As stated above, there is nothing in the prior art that directly links MPIF-1 levels with sepsis, although it is linked with inflammation. TNF-R1 is linked with sepsis, but also with other conditions. Kimura *et al.* (British J. Surg., 85:1631-1635, 1998) showed that TNF-R1 is produced in response to surgical stress, and may be further enhanced by intraoperative bacterial translocation. They suggest that plasma TNF-R1 concentrations may be predictive of postoperative infectious complications (including peritoneal abscess and pneumonia, which are not necessarily conditions of sepsis) (see Table 1 and page 1634, final paragraph). Dollner *et al.* (Biol. Neonate, 80:41-47, 2001) showed that both neonates suffering from various non-infected conditions (such as respiratory distress, intraventricular haemorrhage, and icterus neonatorum) as well as neonates with infection, had higher TNF-R1 (also known as p55) levels than healthy controls (see Table 3). Doellner *et al.* (Early Human Dev., 52:251-261, 1998) attempted to use serum concentrations of TNF-R1 as a diagnostic indicator of sepsis in neonates. However, they found that the specificity of TNF-R1 concentrations was low. They stated, "our data do not suggest that assessment of sTNFR may improve the accuracy of diagnosing early onset neonatal sepsis compared to using CRP. The usefulness of sTNFR as diagnostic tests for infection later in the neonatal period remains to be elucidated" (page 259, final paragraph). Slotwinski *et al.* (J. Clin. Immunol., 22:289-296, 2002) used TNF-R1 to predict local infective complications after colorectal surgery. Slotwinski *et al.* found that TNF-R1 was significantly elevated immediately after liver resection, as well as in patients with post-operative complications (page 295, paragraph 1). These references show that MPIF-1 and TNF-R1 levels are not predictably

correlated with sepsis. In addition to the above references, other authors have also shown MPIF-1 in particular to be elevated in conditions other than sepsis. For example, Hurst *et al.* (Am. J. Respir. Crit. Care Med., 174:867-874, 2006) showed that MPIF-1 was elevated in patients with chronic obstructive pulmonary disease.

It is clear from the art and the specification that both MPIF-1 and TNF-R1 are involved in the inflammatory process. However, both of these cytokines are known to be involved, not just in systemic inflammation, but in local inflammation. The specification does not provide guidance showing the levels of either cytokine that are necessary to for a diagnosis of sepsis, and no means has been provided to differentiate between the increase in cytokines associated with trauma, burns, or other infections and the increase associated with sepsis. In fact, the specification shows that, in two studies, TNF-R1 was not found to be associated with sepsis, while MPIF-1 had a different association with sepsis, depending on the sample source. It is suggested in the specification that TNF-R1 was not identified in studies 1 or 2 because these studies were smaller and because, in study 3, the patients had more severe sepsis than those in studies 1 and 2.

However, the specification does not describe any reference concentration for MPIF-1 or TNF-R1 and does not describe what concentrations of these cytokines are indicative of the presence of severe sepsis. The fact that these markers are present in multiple diseases, such as chronic obstructive pulmonary disease or osteoarthritis complicates matters even further.

When one considers the teachings of the specification and the relevant art, one could not immediately envisage what concentration, relative to the "reference concentration" is indicative of severe sepsis, and the specification lacks any description of these concentrations.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian J Gangle/
Examiner, Art Unit 1645

/Robert B Mondesi/
Supervisory Patent Examiner,
Art Unit 1645